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pQTL-driven Bayesian Network Reveals Genetic Architecture in CSF Proteomics

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THE SWEDISH
BioFINDER STUDY™

Introduction

- Proteomics can capture disease-relevant molecular changes in neurodegeneration.
- Protein quantitative trait loci (pQTLs) provide genetic anchors for interpreting protein regulation.
- Network analysis can reveal coordinated protein changes across biological pathways.
- We built a BioFINDER proteogenomic resource integrating proteomics and genetics.
- We used this resource for pQTL mapping and ongoing genetics-informed network analysis.

BioFINDER proteogenomic database

Develop a database for interpreting BioFINDER protein pQTLs across CSF and plasma.

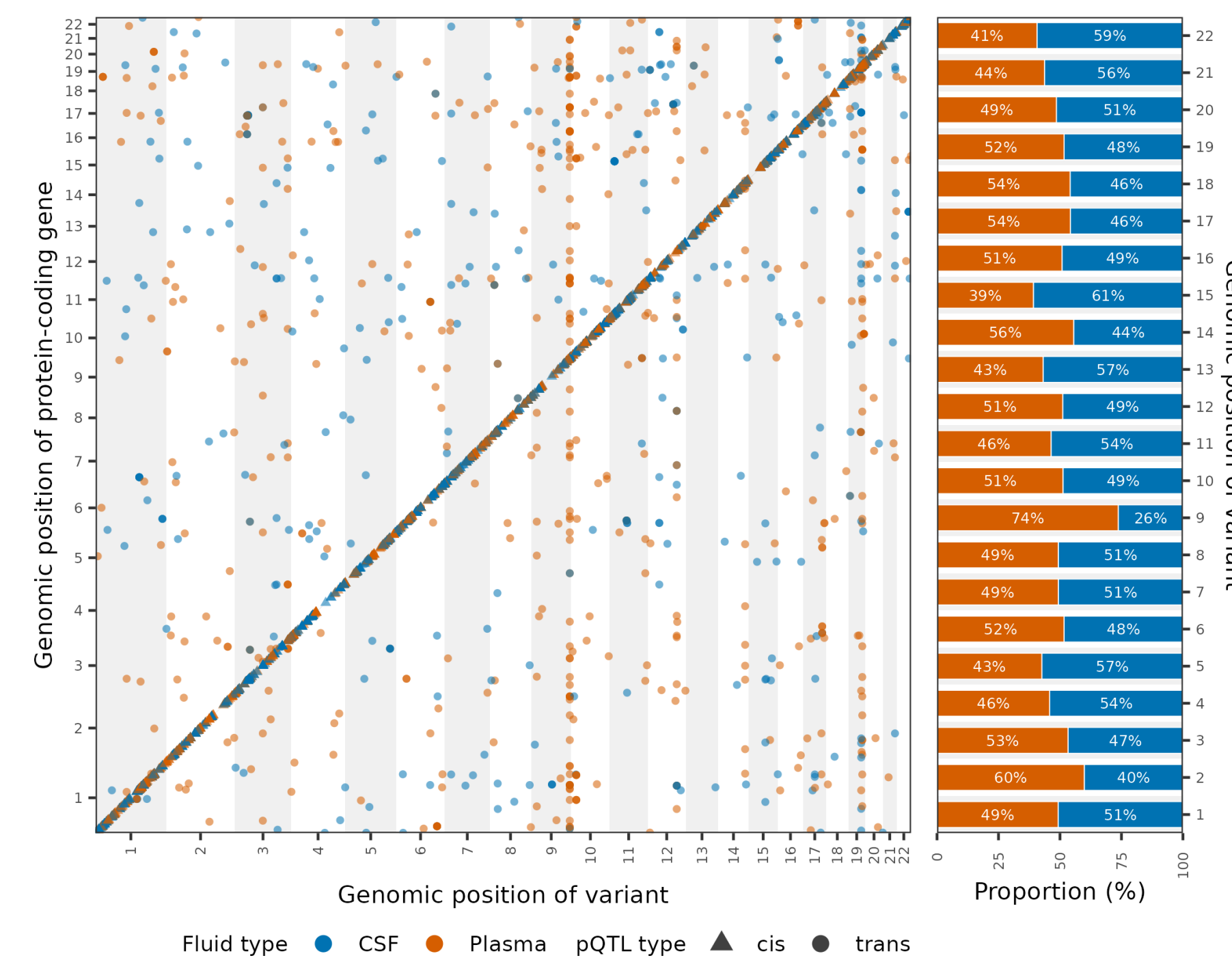
- Integrates in-house proteomics with public genetic resources.
- Fine-mapped pQTL discovery across CSF and plasma.
- QTL colocalization within gene, protein, and diseases.
- Causal effect inference with Mendelian randomization.



Widespread genetic regulation on proteins

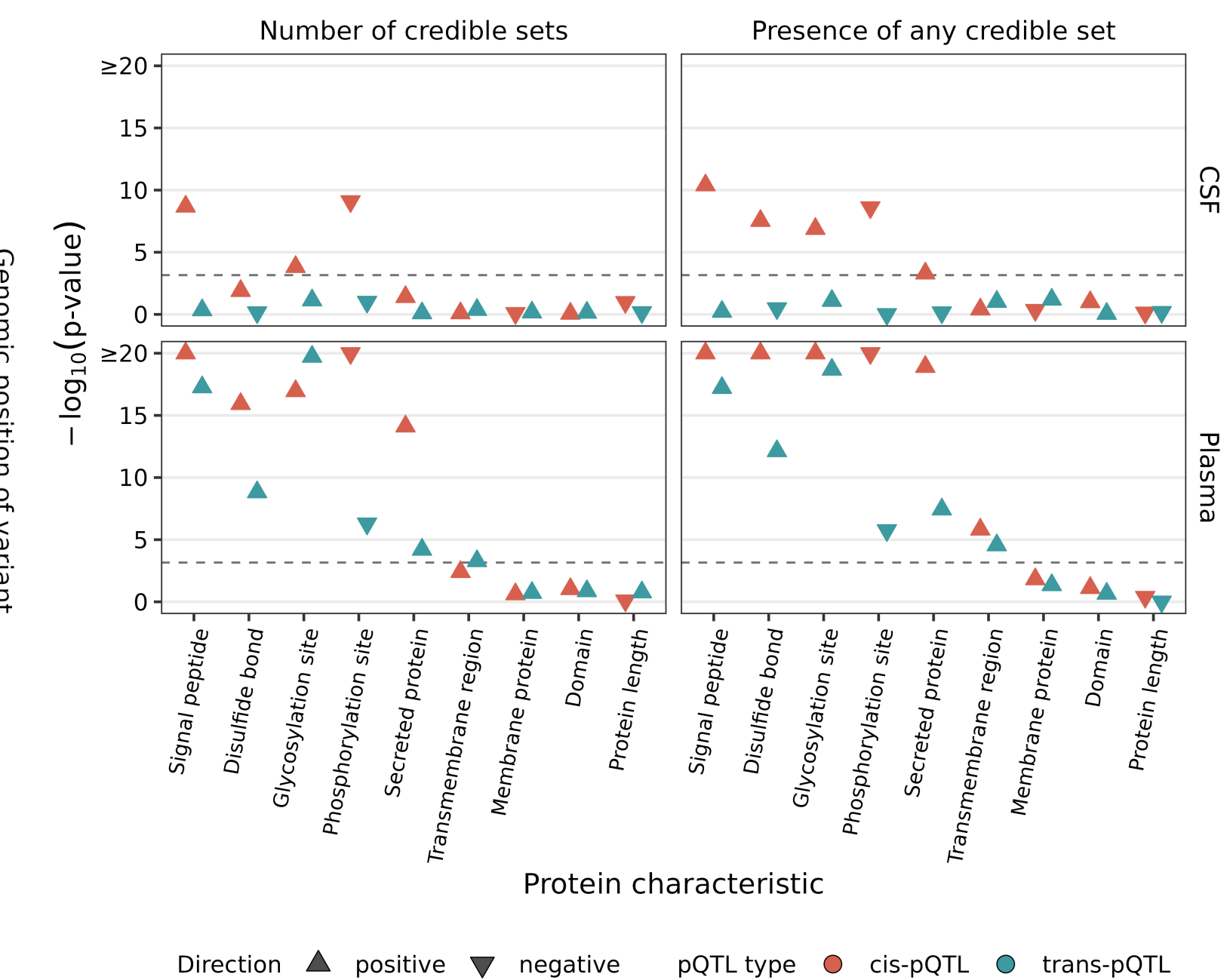
Genome wide pQTL mapping in ~ 1.8k samples

- ~1.4k CSF and ~2.1k plasma proteins in Olink and NULISA.
- ~1.5k regional sentinel pQTLs at genome-wide significance (LD clumping: 1,000 kb/1 Mb, $r^2 < 0.01$).
- Fine-mapping resolved 2,084 independent 95% credible sets (1,647 cis and 437 trans signals).
- 803 proteins had at least one fine-mapped pQTL.



Protein features in pQTL detection across CSF and plasma

- We tested whether UniProt features were associated with 1) fine-mapped pQTL presence, and 2) number of fine-mapped pQTLs.
- Secreted protein were associated with cis-pQTL detection in both fluids.
- Signal peptides and glycosylation sites were associated to more cis fine-mapped SNPs.
- Trans-pQTL feature associations were mainly observed in plasma.



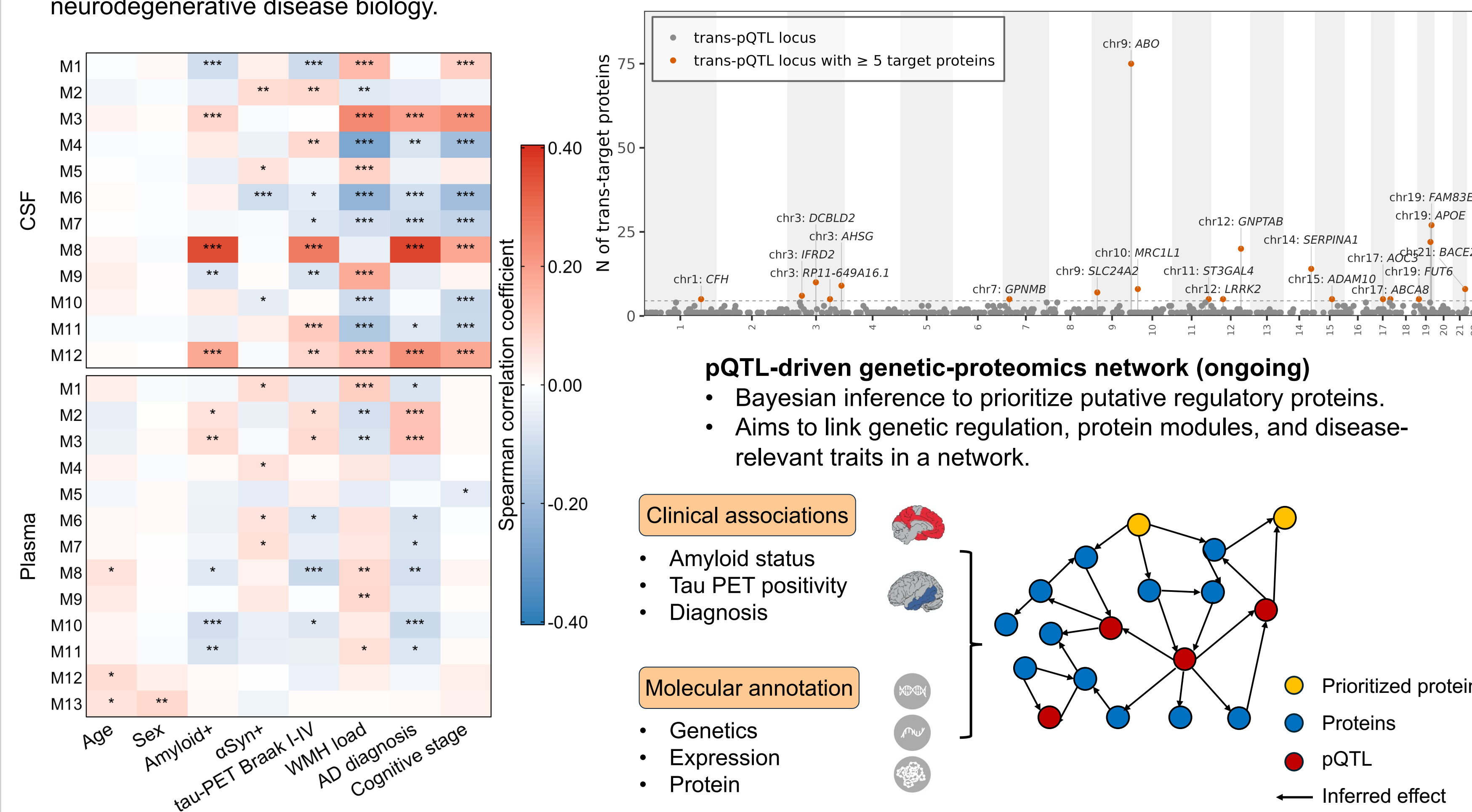
Genetic-proteomics network (ongoing)

Protein modules capture disease-relevant biology

- SpeakEasy detection for CSF and plasma protein modules.
- CSF modules showed stronger associations with AD pathology, cognition, and white-matter lesion load.
- Suggest that CSF modules better capture central neurodegenerative disease biology.

pQTLs as genetic anchors

- Co-expression modules do not define directionality.
- pQTLs affecting multiple proteins can indicate upstream regulation.
- Combining pQTLs with protein modules can guide network modeling.



Conclusion

- We developed a proteogenomic database for protein regulation and genetic interpretation.
- CSF and plasma showed distinct pQTL patterns, suggesting compartment-specific regulation.
- Ongoing network analysis will integrate pQTLs with protein modules to prioritize key regulatory proteins and modules.

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